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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
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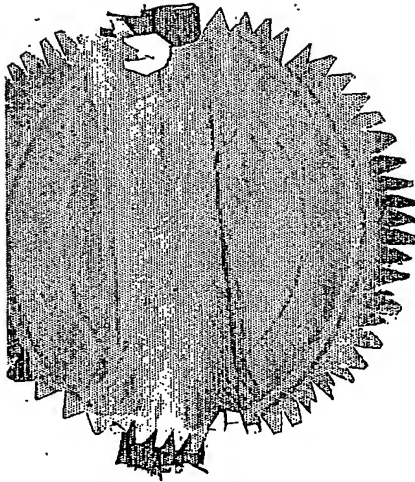
REC'D 03 NOV 2003
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I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application, Provisional Specification and Drawing Sheets filed in connection with Application for Patent No.724/Del/02 dated 8th July 2002.

Witness my hand this 10th day of September 2003.

(S.K. PANGASA)

Assistant Controller of Patents & Designs



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0724-2
08 JUL 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

Patent Office
5000/- cash
8/7/02
265/- in the
Patent Office

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE SYNTHESIS OF NOVEL DIHYDROXYLATED DERIVATIVES OF ATORVASTATIN"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventors for the said invention are

- a. YATENDRA KUMAR
- b. RAM CHANDER ARYAN
- c. KUMAR HARI BHUSHAN
- d. GOWRI SHANKAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 342001 – 10; 8912501-10
Fax No. (91-124) 6342027

ORIGINAL

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, RAM CHANDER ARYAN, KUMAR HARI BHUSHAN, GOWRI SHANKAR of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon-122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a. 
(YATENDRA KUMAR)

b. 
(RAM CHANDER ARYAN)

c. 
(KUMAR HARI BHUSHAN)

d. 
(GOWRI SHANKAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

- a. Provisional Specification (3 copies)
- b. Drawings (3 copies)
- c. Statement and Undertaking on FORM – 3
- d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 682615

dated 17.06.2002 on ANZ Grindlays Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this 8TH day of July, 2002.

For Ranbaxy Laboratories Limited


(S'K PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

0721-2
2002

**PROCESS FOR THE SYNTHESIS OF NOVEL
DIHYDROXYLATED DERIVATIVES OF
ATORVASTATIN**

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the synthesis of novel di-hydroxylated derivatives of structural formula I as shown in the accompanied drawings, which are the putative metabolites of atorvastatin.

Also, novel pharmaceutical compositions comprising the putative metabolites and a method for treating subjects suffering from hypercholesterolemia by administering directly the active metabolite is disclosed.

The compounds of the present invention hold promise to be useful as inhibitors of cholesterol biosynthesis.

Atorvastatin is a member of the class of drugs called statins. Atorvastatin is the only drug in its class specifically indicated for lowering both elevated LDL (Low density lipoprotein) cholesterol and triglycerides in patients with hypercholesterolemia.

Atorvastatin is a selective, competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate limiting hepatic enzyme responsible for converting HMG-CoA to mevalonate, a precursor of sterols including cholesterol. Inhibition of HMG-CoA reductase lowers the amount of mevalonate and subsequently reduces cholesterol levels in hepatic cells. This, in turn, results in upregulation of LDL-receptors and increased hepatic uptake of LDL-cholesterol from the circulation. Atorvastatin ultimately reduces the levels of circulating total cholesterol, LDL-cholesterol, and serum triglycerides. As with other HMG-CoA reductase inhibitors, atorvastatin exhibits no effects on antipyrine hepatic metabolism.

Atorvastatin, ([R-(R*, R*)]-2-(4-fluorophenyl)- β,δ - dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid), depicted in lactone form in Formula II) and its calcium salt trihydrate of formula (III) are well known in the art, and described, inter alia, in U.S. Patents Nos. 4,681,893, 5,273,995.

Atorvastatin is extensively metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. for HMG-CoA reductase is attributed to active metabolites. It is well known in the literature that these compounds are metabolized in vivo to certain phenyl hydroxy

derivatives which are active as parent compound and 70% of the HMG Co-A reductase inhibition associated with atorvastatin has been attributed to its active metabolites. (Drug 1991, 53 (5) 828-847).

US Patent No. 5,385,929 assigned to Warner Lambert Company describes active metabolites of atorvastatin, the hydroxyphenyl compounds of the formula IV as shown in the accompanied drawing as active inhibitor of the biosynthesis of cholesterol which can be administered directly to mammals for treating condition of hypercholesterolemia.

In an already overcrowded field of statins, particularly atorvastatin where a particular chemical modification in the pyrrole nucleus of atorvastatin (US Patent No. 5,385,929) is known to exhibit the same properties as parent compound and the derivatives obtained are known to be useful as inhibitors of cholesterol biosynthesis, we reasoned that a dihydroxy modification of atorvastatin would have an even better water solubility/absorption and expecting to have the activity to reside in the dihydroxy molecule as it may not undergo any further metabolism. and therefore, set out to prepare, hitherto unknown, dihydroxyl derivative of atorvastatin.

The preparation of the compounds of the present invention has been described in the examples and the structures have been shown in the synthetic scheme attached herewith. The protected derivatives of the structural formula I can be deprotected by conventional methods known in the literature.

EXAMPLE 1

Preparation of 4-methyl-3-oxo-N-(2,4-dimethoxyphenyl)-2-(phenylmethylene) pentamide (V)

2,4-dimethoxyaniline (30g, 196 mmol), methyl isobutyryl acetate (25g, 173 mmoles) as 1,2-ethylenediamine (0.1ml) were refluxed together in toluene (150ml) in a flask equipped with dean stark apparatus. Water was removed azeotropically with refluxing for about 5 hours till reaction completion. Reaction mass was cooled to 40°C. Toluene was recovered under reduced pressure to obtain residue which was dissolved in ethyl acetate (200ml). Ethyl acetate layer was washed with diluted HCl (10%, 100ml x 2) and finally with saturated brine (100ml). Organic layer was concentrated under reduced pressure.

Oily mass obtained was taken in toluene (150ml) and to it β -alanine, glacial acetic acid (4.5g) and benzaldehyde (18.33g, 173 mmol) were added. The mixture was refluxed in a flask equipped with dean stark apparatus to remove water azeotropically. After the completion of reaction, solvent was removed under reduced pressure at 40°C to obtain only product having two products (TLC, 20%, Ethylacetate in hexane) R_f – 0.5 and 0.36 respectively and were purified on silica gel column with eluant 10% ethyl acetate in hexane. Both were found to be isomers. Product of R_f = 0.5 was characterized by spectral data as given below and was taken over for further reaction.

Mass ($M^+ + 1$); 354

^1H NMR, CDCl_3 (δ , ppm): 1.04 (d, 6H), 2.60 (septet, 1H) 3.81 (s, 3H), 3.92 (s, 3H), 6.5 (br s, 2H), 7.28-7.4 (m, 5H), 8.10 (s, 1H), 8.31 (d, 1H) and 9.24 (s, 1H)

IR (KBr) cm^{-1} : 3320, 2965, 1684, 1602, 1536, 1466, 1415, 1304, 1222, 1204

EXAMPLE 2

Preparation of 4-methyl-3-oxo-N-(2,6-dimethoxyphenyl)-2-[1-phenyl-2-(4-fluorophenyl)-2-oxo-ethyl]pentamide (VI)

Product from Example 1 of R_f -0.5 (9.0g, 25.5 mmole) was taken isopropyl alcohol (27ml) and to it 4-fluorobenzaldehyde (3.42g, 27.6 mmol) and triethyl amine (2.88g, 28mmol) were added followed by 3-ethyl-5-[2-hydroxyethyl]-4-ethylthiazolium bromide (7.0g). Reaction was refluxed for about 16 hour at 80-81° till reaction completion. Reaction mixture was cooled to RT and solid product was filtered and washed with cold isopropyl alcohol (10ml x 2). Product was dried under reduced pressure of <10mm/hg at 50°C (6.8g).

Mass ($M^+ + 1$); 478

^1H NMR, DMSO-d_6 (δ , ppm): 1.13 (d, 3H), 1.24 (d, 3H) 2.97 (septet, 1H), 3.75 (s, 6H), 4.53 (d, 1H), 5.36 (d, 1H) 6.36 – 6.39 (m, 2H), 7.03 (t, 2H), 7.15 – 7.35 (m, 5H) 7.48 (s, 1H), 7.83 (d, 1H), 7.99 (dd, 2H)

IR (KBr) cm^{-1} : 3219, 3038, 2965, 1718, 1690, 1648, 1596, 1514

EXAMPLE 3

Preparation of (2R-trans)-5-(4-fluorophenyl)-2-[1-methylethyl)-N-(2,4-dimethoxyphenyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1H pyrrole -3-carboxamide (VII)

Product from Example 2 (6.5g, 13.62 mmol) was taken in a solvent mixture (65ml) of heptane, toluene and tetrahydrofuran in ratio of 4:1:1 respectively. To this a side chain amine derivative i.e. (4R,cis)-1,1-dimethylethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (prepared as mentioned in lit.) 4.4g, 16.11 mmol was added followed by addition of pivalic acid (1.54g, 14.9 mmol). The reaction mixture was refluxed at 85-90°C for 48 hours. After the completion of the reaction, it was cooled to room temperature. Diethyl ether (65ml) was added to reaction mass and which was washed with 1N-HCl (50 ml) followed by saturated sodium bicarbonate solution (50ml). Organic layer was concentrated under reduced pressure and residue dissolved in methanol (200ml) water (50ml) and conc. hydrochloric acid (10ml) were added to above methanolic solution. Stirred the mixture for 5 hours. Methanol was removed under reduced pressure. Extracted the oily product in ethyl acetate. Ethyl acetate layer was concentrated under reduced pressure to obtain oily mass (9.0gm), which was dissolved in methanol (100ml) and to this sodium hydroxide solution (2g in 100ml water) was added. Stirred the reaction mixture at room temperature for 5 hours. Methanol was recovered under reduced pressure. Aqueous layer was washed with diethyl ether. Aqueous layer was acidified to pH 2-3 with dil. HCl. Product was extracted with ethyl acetate (100ml). Ethyl acetate layer was concentrated under reduced pressure to obtain semi solid product (4.6g).

EXAMPLE 4

Preparation of 7[3-(2,4-dimethoxy-phenylcarbamoyl)-5-(4-fluorophenyl)-2-(1-methylethyl)-4-phenyl-pyrrol-1-yl]-3R, 5R-dihydroxy-heptanoic acid sodium salt (I)

Sodium hydroxide (0.2g, 5.0 mmol) was dissolved in methanol (30ml). To this alkaline solution, compound from Example 3 (3.0g, 4.85 mmol) was added and stirred at room temperature for 5 hours. Methanol was removed under reduced pressure. Residue was triturated with diethyl ether to obtain solid product, which was filtered and washed with

diethyl ether (5ml x 2). Product was dried under reduced pressure of <10mm/ at 50°C to obtain dried product (3.0g).

Mass ($M^+ + 1$); 619

¹H NMR, DMSO- d_6 (δ , ppm): 1.1-1.2(m, 1H), 1.28-1.40 (m, 1H), 1.41 (d, 6H), 1.5-1.65 (m, 2H), 1.77 (dd, 1H) 1.98 (dd, 1H), 3.38 (septet, 1H), 3.5 (s, 3H & m, 1H), 3.7 (s, 3H), 3.72 – 3.82 (m, 1H) 3.87 – 4.03 (m, 2H), 6.4-6.5 (m, 2H), 7.0-7.35 (m, 9H), 7.85 (d, 1H), 7.89 (s, 1H).

IR (KBr) cm^{-1} : 3200, 1658, 1567, 1523, 1412

EXAMPLE 5

Preparation of 7-[3-(2,4-dimethoxyphenyl carbamoyl)-5-(4-fluorophenyl)-2-(1-methylethyl)-4-phenyl-pyrrol-1-yl]-3R, 5R-dihydroxy-heptanoic acid calcium salt

Sodium salt from example 4 (1.0g) was dissolved in water (10ml) at 50°C. To this solution, calcium acetate solution (0.2g in 2ml of water) was added and stirred for 30 min at room temperature. Solid obtained was filtered and washed with water (5ml). Dried the solid product under reduced pressure of <10mm / Hg at 60°C to obtain calcium salt of the product (0.75mg).

Mass ($M^+ + 1$); 619

¹H NMR, DMSO- d_6 (δ , ppm): 1.15 – 1.30 (m, 2H), 1.39 (d, 6H), 1.5-1.67(m, 2H), 1.92 (dd, 1H) 2.06 (dd, 1H), 3.3 (septet, 1H), 3.5 (s, 3H and m, 1H), 3.69 (s, 3H), 3.65-3.8 (m, 1H), 3.9 – 4.08 (m, 2H), 6.4-6.5 (m, 2H), 7.0 – 7.32 (m, 9H), 7.85 (d, 1H), 7.89 (s, 1H)

IR (KBr) cm^{-1} : 3150, 1653, 1558, 1521, 1433

Dated this 8TH day of July, 2002.

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

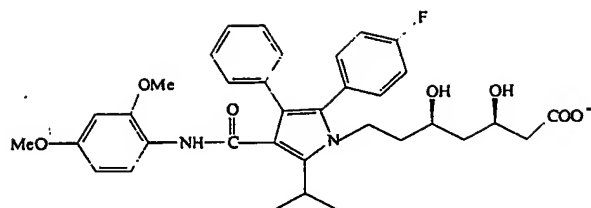
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Application No.

Sheet 01 of 05

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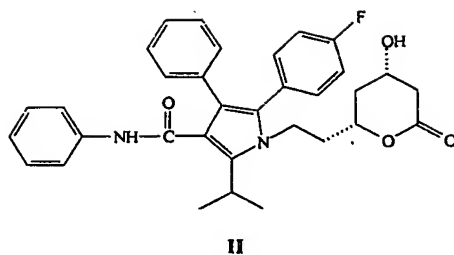
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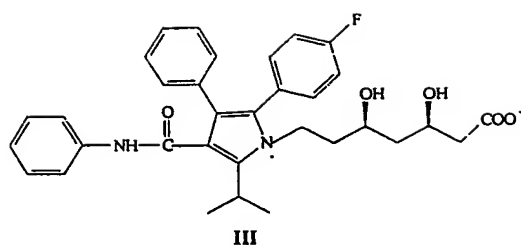

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Application No.

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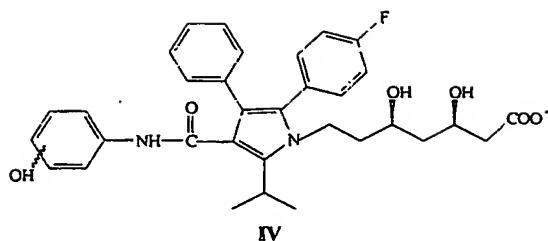

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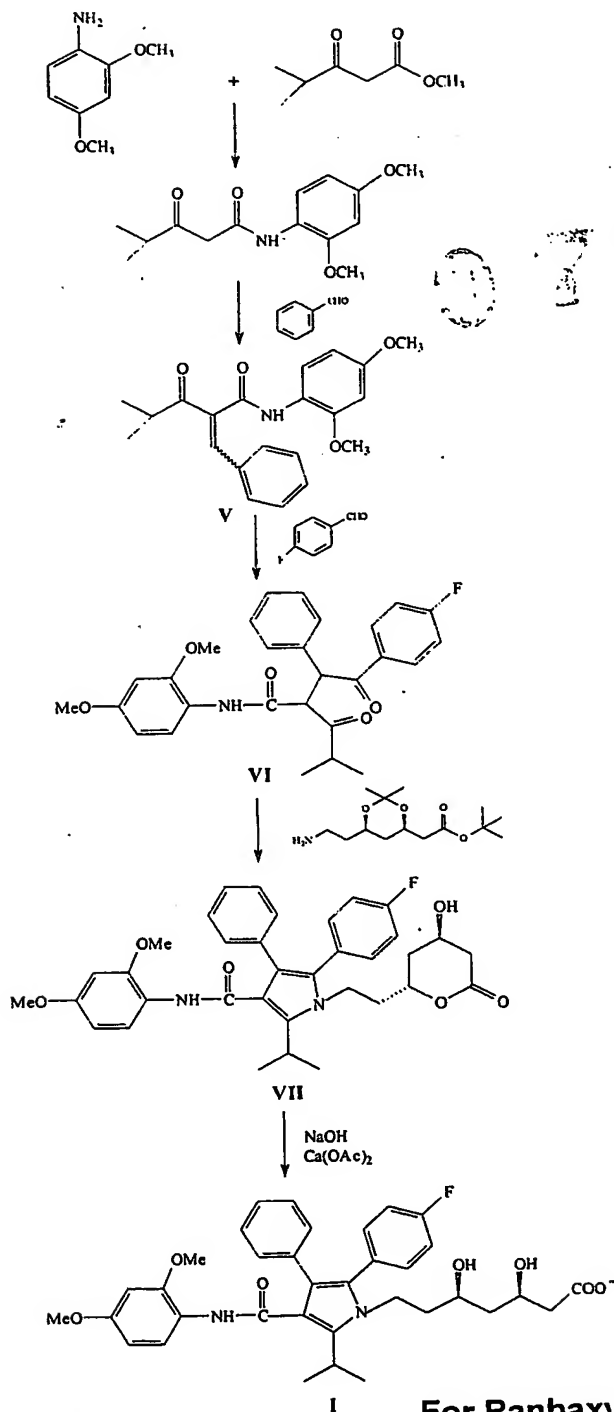
Sheet 04 of 05



For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

Scheme - I



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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